

PATENT COOPERATION TREATY

MAY 10 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYTo:
JANE MASSEY LICATA
LICATA & TYRRELL P
66 E. MAIN STREET
MARLTON, NJ 08053Docket System ☒Status Report ☒Docket Book ☒

6/6/04 WO

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing
(day/month/year)

06 MAY 2004

Applicant's or agent's file reference

ISPH-0672WO

REPLY DUE

within 2 months/days from
the above date of mailing

International application No.

PCT/US03/18320

International filing date (day/month/year)

10 June 2003 (10.06.2003)

Priority date (day/month/year)

11 June 2002 (11.06.2002)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C12Q 1/68; A01N 43/04; C07H 21/04; A61K 31/07 and US Cl.: 514/44; 536/24.5, 23.1, 24.33; 435/325, 6, 91.1, 375

Applicant

ISIS PHARMACEUTICALS, INC.

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I ☒ Basis of the opinionII ☐ PriorityIII ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV ☐ Lack of unity of inventionV ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI ☐ Certain documents citedVII ☐ Certain defects in the international applicationVIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.**Also** For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6**If no reply is filed**, the international preliminary examination report will be established on the basis of this opinion.4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 11 October 2004 (11.10.2004).

Name and mailing address of the IPEA/US

Mail Stop PCT, Attn: IPEA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Terra C. Gibbs

Telephone No. (571) 272-0564

Form PCT/IPEA/408 (cover sheet)(July 1998)

WRITTEN OPINION

International Application No.

PCT/US03/18320

I. Basis of the opinion

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☒ the description:
 - pages 1-25, as originally filed
 - pages NONE, filed with the demand
 - pages NONE, filed with the letter of _____
- ☒ the claims:
 - pages 26-28, as originally filed
 - pages NONE, as amended (together with any statement) under Article 19
 - pages NONE, filed with the demand
 - pages NONE, filed with the letter of _____
- ☐ the drawings:
 - pages NONE, as originally filed
 - pages NONE, filed with the demand
 - pages NONE, filed with the letter of _____
- ☒ the sequence listing part of the description:
 - pages 1, as originally filed
 - pages NONE, filed with the demand
 - pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE _____
- ☐ the claims, Nos. NONE _____
- ☐ the drawings, sheets/fig NONE _____

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."

WRITTEN OPINION

International application No.
PCT/US03/18320

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims <u>5-16</u>	YES
	Claims <u>1-4</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-16</u>	NO
Industrial Applicability (IA)	Claims <u>1-16</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-16 meet industrial applicability as defined by PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Claims 1-4 lack novelty under PCT Article 33(2) as being anticipated by Windmeier et al. (Biochemical Pharmacology, 1996 Vol. 51:577-584).

Windmeier et al. disclose cultured fat-storing cells exposed to pentoxifylline (see Table 1). The specification, at page 8, lines 22-27 teaches that pentoxifylline is a non-specific phosphodiesterase inhibitor that inhibits the production of IL-12 p35 subunit, but not IL-12 p40 subunit. Therefore, Windmeier et al. anticipate claims 1-4.

Claims 1-4 lack novelty under PCT Article 33(2) as being anticipated by Cigolini et al. (Artherosclerosis, 1999 Vol. 143:81-90).

Cigolini et al. disclose human adipose tissue treated with pentoxifylline (see Figure 9). Therefore, Cigolini et al. anticipate claims 1-4.

Claims 1-16 lack an inventive step under PCT Article 33(3) as being obvious over Baker et al. [U.S. Patent No. 6,399,379], in view of Gately et al. [WO 99/37682].

Baker et al. teach antisense modulation of IL-12 p35 subunit in cells or tissues in vitro or in vivo comprising the administration of antisense oligonucleotides targeted to IL-12 p35 subunit.

Gately et al. teach anti-human IL-12 antibodies that are characterized by specificity to the IL-12 heterodimer, but do not bind to the IL-12 p40 subunit.

It would have been obvious to devise a method for inhibiting the differentiation of an adipocyte cell comprising contacting a preadipocyte cell with an inhibitor of IL-12 p35 subunit, using the method taught by Baker et al. and the motivation of Gately et al. One of ordinary skill in the art would have substituted the antisense oligonucleotides targeted to IL-12 p35 subunit taught by Baker et al. with the IL-12 antibodies taught by Gately et al. because the IL-12 antibodies have been demonstrated to neutralize the biological activity of IL-12 p35 subunit specifically, as opposed to IL-12 p40 subunit, since the two exist as a heterodimer.

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.